Title

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Journal

International Journal of Radiation Oncology • Biology • Physics, 86(4)

ISSN

0360-3016

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Publication Date

2013-07-01

DOI

10.1016/j.ijrobp.2013.03.034

Peer reviewed

Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2013 July 15; 86(4): 649–655. doi:10.1016/j.ijrobp.2013.03.034.

Radiation, Atherosclerotic Risk Factors and Stroke Risk in Survivors of Pediatric Cancer: a Report from the Childhood Cancer Survivor Study

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Abstract

Background—The impact of childhood cranial radiation therapy (CRT) on stroke risk in adulthood, and the role of modifiable atherosclerotic risk factors, remains poorly defined. We assessed long-term incidence rates and stroke risk factors in survivors of childhood cancer followed by the Childhood Cancer Survivor Study (CCSS).

Patients and Methods—CCSS is a multi-institutional retrospective cohort study of 14,358 five-year survivors of childhood cancer and 4,023 randomly selected sibling controls with longitudinal follow up. Age-adjusted incidence rates of self-reported late-occurring (≥ 5 years after diagnosis) first-stroke were calculated. Multivariable Cox Proportional Hazards models were used to identify independent stroke predictors.

Results—During a mean follow-up of 23.3 years, 292 survivors reported a late-occurring stroke. The age-adjusted stroke rate per 100,000 person-years was 77 (95% Confidence Interval [CI] 62–96) compared to 9.3 (95% CI 4–23) for siblings. Treatment with CRT increased stroke risk in a dose dependent manner: hazard ratio (HR) 5.9 (95% CI 3.5–9.9) for 30–49 Gy CRT, and 11.0 (7.4–17.0) for 50+ Gy CRT. The cumulative stroke incidence in survivors treated with 50+ Gy CRT was 1.1% (95% CI 0.4–1.8) at 10 years post-diagnosis and 12% (95% CI 8.9–15.0) at 30

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Conflict of Interest: None of the authors have any conflict of interest to report.

years. Hypertension (HTN) increased stroke hazard by 4-fold (95% CI 2.8–5.5) and in black survivors by 16-fold (95% CI 6.9–36.6).

Conclusion—Young adult pediatric cancer survivors have an increased stroke risk that is associated with CRT in a dose dependent manner. Atherosclerotic risk factors enhanced this risk and should be treated aggressively.

Introduction

Stroke is a disabling consequence of childhood cancer—and childhood cancer treatment—that remains poorly understood. Previous studies have shown that children treated for central nervous system (CNS) tumors or other cancers carry a significantly increased stroke risk, and that cranial radiation therapy (CRT) is a particularly strong predictor of this risk (1–3). However, the mechanism by which CRT increases stroke risk in cancer survivors is not fully understood. Current literature has focused on arteriopathies such as moyamoya that develop within the relative short-term after CRT (4, 5). Atherosclerosis, the most common etiology of stroke in adults, is a known sequelae of radiation therapy (6). Hence, it is plausible that CRT in childhood initiates accelerated intracranial atherosclerosis and thereby increases long-term stroke risk as childhood cancer survivors age. A better understanding of this relationship between CRT, atherosclerotic risk factors, and long-term stroke risk is crucial for the development of primary stroke prevention strategies in this high-risk group.

The Childhood Cancer Survivor Study (CCSS) provides a unique opportunity to study late effects in pediatric cancer survivors. Within this cohort we tested the hypotheses that a) the increased risk of stroke conferred by childhood CRT persists into adulthood; and b) atherosclerotic risk factors further increase the stroke risk in cancer survivors.

Material and Methods

Sample Characteristics

CCSS is a retrospective cohort of childhood cancer survivors (survival ≥ five years after diagnosis) diagnosed between January 1, 1970 and December 31, 1986 with longitudinal follow-up. Eligibility criteria for enrollment in CCSS included common pediatric cancer diagnoses, age < 21 years at diagnosis, and survival greater than five years after diagnosis. A detailed description of the cohort is provided elsewhere (7) and available online (www.ccss.stjude.org). Appropriate institutional approval was in place and participants consented to be part in this study.

Data Collection

Clinical data regarding the cancer diagnosis and treatment were collected at enrollment. CCSS participants (or their proxy) periodically completed comprehensive questionnaires including information on demographics and medical conditions (for details see www.ccss.stjude.org/documents/original-cohort-questionnaires). The primary outcome was first late-occurring stroke (≥ 5 years post diagnosis), which was assessed at baseline in 1994, and on follow up questionnaires administered in 2000–2002 and 2007–2009. Stroke and age at first occurrence of stroke were self-reported. Stroke outcome was defined as the earliest report of stroke in a time-to-event analysis. Subjects who had a stroke prior to 5 years post-diagnosis were not included in the time-to-event analysis. Information on the specific location or type of stroke was not available. Radiation records were reviewed for 98% of the 8510 participants known to have radiation therapy. Direct radiation to the brain was assessed for four segments as outlined elsewhere (8). If at least half of the segment was included in the treatment field, the segment was assigned maximum treatment dose. Indirect radiation treatment was also categorized (treatment to the head and/or neck, but no treatment to the

brain, or treatment to the trunk or limbs - spine for CNS patients). Atherosclerotic and other stroke risk factors such as hypertension (HTN), diabetes mellitus, history of smoking, and use of oral contraceptive pills (OCP) are based on questions asking about the earliest occurrence of these morbidities. Hyperlipidemia was not consistently captured within the CCSS and therefore not included in the analysis. Medication use associated with these morbidities (e.g. insulin or blood pressure medications) was considered for classification, with onset determined by reported age at first use, or age at completion of the earliest questionnaire indicating use of such medication. History of NF1 was assessed by asking about congenital or hereditary conditions.

Statistical Analyses

For patients with self-reported stroke but unknown age at occurrence (n=18), multiple imputation methodology was used to create 10 imputed values for each missing age based on treatment information. Reported analytic results were obtained by combining analyses across the imputed data sets using standard formulas (9).

Survivor person-years were calculated from five years past cancer diagnosis to date of first self-reported stroke, death or last follow-up. For siblings, person-years were calculated starting at five years from date of birth. Observed incidence rates for stroke occurrence per 100,000 person-years were assessed by Poisson regression. Additional models estimated relative risk (RR) for survivor stroke compared to siblings, with robust variance estimates to account for within-family correlation (10). Models were adjusted for gender and with a cubic spline for age, and parameter estimates from the models were used to calculate predicted incidence rates per 100,000 person-years for females at the median age of 23 years.

Cox proportional hazard models, with age as the time scale, assessed risk factors for hazards of stroke among survivors and report hazard ratios (HR) and associated confidence intervals (CI). Age as timescale was used as stroke risk increases with age (11). Univariate models examined demographics such as race and gender, age at diagnosis, year of diagnosis, recurrence, chemotherapy, and CRT. Neck irradiation was evaluated as any versus none. The majority of subjects (95%) were irradiated at time of diagnosis and therefore we used age at diagnosis to evaluate impact of age at time of CRT. Brain radiation dosages were divided into 5 categories including: 50+ Gy, 30–49 Gy, 1.5 to 29 Gy, indirect radiation and no radiation. Known stroke risk factors such as HTN, history of smoking, diabetes mellitus, neurofibromatosis 1 (NF1) and the use of oral contraceptives (OCP) were also examined. HTN, diabetes mellitus, OCP use, recurrence and smoking were treated as time-varying covariates, based on the earliest reported age.

Multivariable Cox regression was used to develop final models of predictors of stroke. Covariates were assessed in a stepwise fashion starting with those significant in the univariate models at $\alpha \leq 0.10$. Final models retained covariates significant at $\alpha \leq 0.05$, plus gender, age at diagnosis, diabetes, HTN and race as a priori covariates. Radiation doses to the four brain segments were assessed in separate models but no significant differences were found between brain segment results. Final models proceeded with only maximum dose to the brain. In an exploratory risk factor analysis, two way interactions were tested for all significant and a priori covariates in the multivariable model. For significant interactions, composite variables were created to represent combinations of the levels. Cumulative incidence curves for stroke, starting at five years after cancer diagnosis, were constructed for each disease group, treating death as a competing risk event.

Analyses were first conducted on the entire cohort. Since a large number of strokes were found in CNS tumor survivors, sub-analysis were conducted in this group to rule out

potential confounding as CNS tumor survivors could be at a higher stroke risk independent of CRT.

All reported *P* values are two-sided and were considered significant at $\alpha = 0.05$, with the exception of interactions, for which $\alpha = 0.10$ was used.

Results

This study included a total of 14,358 childhood cancer survivors, followed for a mean of 23.3 years post-diagnosis, and 4,023 sibling controls. Detailed demographics are listed in Table 1. Table 2 lists specific cancer diagnoses and number of participants per cancer type.

First late-occurring Stroke in Childhood Cancer Survivors

A total of 292 late-occurring strokes were identified in this cohort with a RR of 7.8 (95% CI 4.7–13.0; $P<0.001$) compared to siblings (Table 2). Mean time from diagnosis to late-occurring stroke was 18.6 years (range 5.2–38.1 years). Median age at first late-occurring stroke was 28.5 years (Interquartile Range [IQR] 19–36).

Since almost 50% of new occurring strokes were reported on the most recent survey performed in 2007–09 we assessed potential misreporting on prior questionnaires. We identified only 19 participants that had stroke ages that happened before completion of the prior survey in 2000.

Stroke Predictors in Childhood Cancer Survivors

In the univariate models, significant stroke predictors were CRT, HTN, diabetes mellitus and history of recurrence. Black race also increased stroke risk two-fold compared to non-Hispanic whites. Surprisingly neck irradiation did not increase the stroke risk (RR 1.3 (95% CI 1.0–1.7); p=0.07). Of 57 patients with a history of NF1, only 3 patients reported a late occurring stroke: one occurred in a patient with HD 15 years after initial cancer diagnosis and one in a patient with CNS tumor 32 years after initial cancer diagnosis. For the third patient who had a history of sarcoma, the time to stroke was imputed with a mean age of 11 years post diagnosis.

In the multivariable analysis, CRT remained an independent stroke predictor with a dose-dependent effect (Figure 1A; Table 3). Survivors with HTN were four-fold more likely to report a stroke compared to survivors without HTN (HR 4.0, 95% CI 2.8–5.5; $P<0.001$). There was a significant interaction between HTN and black race ($P=0.058$ for the test for interaction); both of these conditions were present in 113 patients. We generated a race/HTN composite variable to better demonstrate the combined effect on stroke risk (Table 3).

Survivors demonstrated increased stroke risk with duration of survival time (Figure 1A). Among those patients who received the highest CRT dose (50+ Gy), the cumulative incidence of stroke increased from 1.1% (95% CI 0.4–1.8) at 10 years to 11.9% (95% CI 8.9–14.9) 30 years post diagnosis.

First late-occurring Stroke in CNS Tumor Survivors

Almost half of the strokes (125 of 292; 42.8%) were reported in CNS tumor survivors who constituted only 13.1% of the cohort (Table 2). Amongst these, mean time from diagnosis to late-occurring stroke was 18.6 years (range 5.2–36.8 years) at a median age of 27 years (IQR 19–35).

There were no significant differences in rates of stroke between CNS diagnosis types (data not shown)

Stroke Predictors in CNS Tumor Survivors

In the univariate analysis, CRT, HTN and diabetes mellitus were significant predictors of stroke. A dose-dependent effect was again observed (Figure 1B). Neck irradiation did not increase the stroke risk significantly (RR 1.0 (95% CI 0.7–1.6); p=0.84).

In the multivariable analysis, treatment with CRT (50+ Gy) and HTN were independent predictors of late-occurring stroke (Table 4). We found an interaction between HTN and diabetes mellitus (P=0.057 for test for interaction). Both conditions were present in 21 patients. The combination of diabetes mellitus and HTN increased stroke hazard 14-fold (Table 4). Age at diagnosis, with the intrinsic adjustment for current age in the Cox model with age as the time scale, did not influence the risk of late-occurring stroke.

Similar to the full cohort within the 50+ Gy group, the cumulative incidence of late-occurring stroke increased from 1.3% (95% CI 0.4–2.1) at 10 years to 14.2% (95% CI 10.5–17.9) at 30 years post diagnosis (Figure 1B).

DISCUSSION

Our study of 14,358 pediatric cancer survivors followed by the CCSS assessed the incidence of self-reported late-occurring stroke and stroke predictors. We found that CRT is a particularly strong stroke predictor in these cancer survivors, an effect that is dose dependent and increases with time from diagnosis. Further, atherosclerotic risk factors such as HTN increased this risk significantly, especially in black pediatric cancer survivors.

CRT has been shown to be a significant stroke predictor in earlier CCSS reports of leukemia and CNS tumor survivors (2). However, the question remained as to whether stroke risk continues to increase the further these individuals are from treatment. Of the 292 late-occurring strokes in this study, 129 (44%) were new cases reported on the 2007 follow up. Among young adult survivors treated with 50+ Gy CRT, we found the cumulative incidence of stroke increased 12-fold between 10 and 30 years post diagnosis. This suggests that the elevated stroke risk conferred by childhood CRT not only persists into early adulthood but also continues to increase decades after treatment.

CRT has been shown to increase the risk of HTN and diabetes in cancer survivors (12). To assess if we underestimated the effect of CRT on stroke risk by including HTN and diabetes in our analysis we excluded these variables in additional models. The effect of CRT on stroke risk did not change (data not shown).

The mechanism by which CRT increases stroke risk is not completely understood. Imaging and animal studies have shown that CRT can lead to a vasculopathy such as moyamoya, which itself confers a higher stroke risk (5, 13). The development of moyamoya occurs relatively early after radiation; it was identified at a median of 55 months after CRT in one report (5). Other reports have shown that neck radiation can accelerate atherosclerosis, which is the leading cause of stroke in the older population (> 60 year) (13, 14). Therefore it is plausible that CRT contributes to the increased stroke risk via two vascular mechanisms: first, through an earlier occurring non-atherosclerotic arteriopathy, labeled moyamoya in its most severe form, and second, via a later appearing arteriopathy in the form of accelerated intracranial atherosclerosis.

A role for atherosclerosis in the delayed stroke after CRT would have important implications on how childhood cancer survivors should be managed. In the general population, the underlying etiology of stroke in young adults differs from the older population (> 60 years), with atherosclerosis only accounting for a minority of stroke cases in patients < 44 years of

age (15). In our cohort, the strokes occurred at a median of 29 years of age, yet atherosclerotic risk factors appeared to play a role: HTN increased the stroke risk in the full cohort, and diabetes mellitus in combination with HTN had a strong effect on stroke risk in CNS tumor survivors. In addition, we found that black childhood cancer survivors with HTN are at a particular high stroke risk compared to other races, which is in concordance with published reports that demonstrate a higher prevalence of atherosclerotic risk factors in blacks (16, 17). These findings support our second hypothesis that atherosclerotic risk factors increase the stroke risk in cancer survivors at a much younger age (< 30 years of age) compared to the general population and that these need to be monitored and treated aggressively.

By whom, when and where pediatric cancer survivors should be followed is not well defined (18). The Children's Oncology Group recommends screening for HTN as well as fasting blood glucose and lipid profile every two years in overweight/obese children treated with CRT. Based on the significantly elevated stroke risk found in childhood cancer survivors, especially those treated with CRT, it is important that patients, families and medical personnel are aware of the elevated stroke risk and the contribution of modifiable stroke risk factors.

Surprisingly, we did not find an association between age at diagnosis and the risk of late-occurring stroke. Fouladi et al. reported that age less than five years at the time of CRT was the most predictive factor for the development of lacunar strokes thought to be due to a small vessel vasculopathy. However, their study included strokes occurring at any time after diagnosis, while our study analyzed only late-occurring strokes (19). In addition, our study controlled for current age by using age as the time scale in the Cox regression models, possibly better accounting for this source of confounding. Additional research is required to assess if, and how, age changes the susceptibility of radiation associated vascular injury.

Our study is limited by the fact that strokes were self-reported and no brain imaging was available for review. However, we estimated a late-occurring stroke rate of 9.3 per 100,000 person-years in siblings a rate that is similar to published annual stroke rates (17, 20). Atherosclerotic risk factors were similarly measured by self-report, and hence there is potential for misclassification of these variables in our study. It is possible that other well-described atherosclerotic risk factors, such a history of smoking, obesity and hyperlipidemia are also contributing to the stroke risk in these pediatric cancer survivors but were not consistently captured in all of the CCSS surveys. Prior studies have shown that there is a significant relationship between overweight and/or obesity and HTN, diabetes mellitus as well as dyslipidemia further supporting that we might underreport on these other well-known atherosclerotic risk factors in our analysis (21, 22). Further, family history of stroke was not assessed by these questionnaires. It is well established that neck irradiation can lead to increased stroke risk in head and neck cancer patients due to early cervical carotid atherosclerosis (6, 23). In this current study neck irradiation was not significantly correlated with risk of late occurring stroke. The assessment of neck irradiation was limited since we did not have access to detailed neck irradiation dosimetry.

We conclude that pediatric cancer survivors treated with CRT are at substantial risk for late-occurring strokes and that this risk is radiation dose dependent and increases with age. Atherosclerotic risk factors such as HTN may increase this stroke risk, especially in black cancer survivors, and should be screened for and treated aggressively as they enter young adulthood.

Acknowledgments

The authors thank the participants and their families for their participation in the CCSS.

Funding Sources: This work was supported by the National Cancer Institute [U24 CA 55727 to L.L.R.], the Cancer Center Support (CORE) [grant CA21765] and the American Lebanese-Syrian Associated Charities (ALSAC). Dr. Mueller and Dr. Fullerton were supported by a private donation from the LaRoche family, the Neurological Sciences Academic Development Award [K12NS001692 to SM], and an independent Scientist Award K02 [NS053883 to HF]. The study sponsors had no impact on study design and data analysis.

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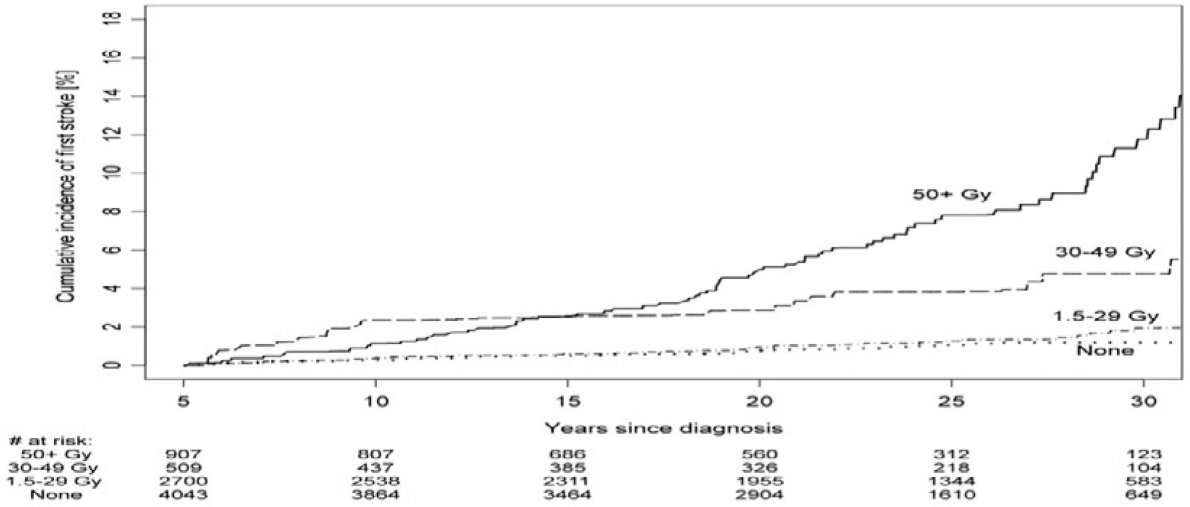
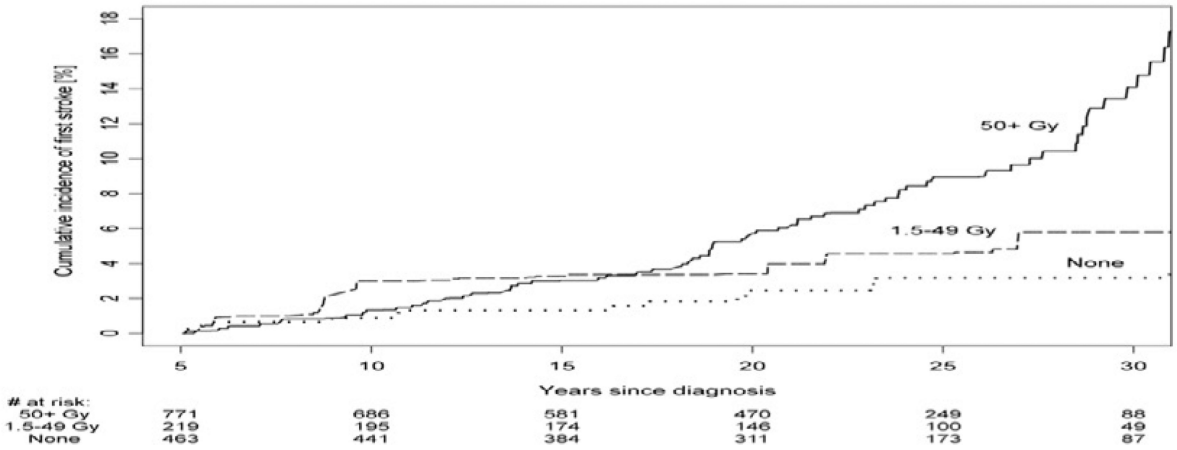
Summary

We evaluated the risk of stroke and associated risk factors in the Childhood Cancer Survivor Study. Within this cohort we demonstrate that treatment with cranial radiation therapy increases the risk of first occurring stroke in a dose dependent manner and show for the first time that atherosclerotic risk factors contribute to this elevated stroke risk, even in young adulthood. Atherosclerotic risk factors should be screened for and treated aggressively in this high-risk group.

(A)



(B)



1. .

(A) Cumulative incidence of late-occurring stroke by dose of maximum CRT in pediatric cancer survivors.

(B) Cumulative incidence of late-occurring stroke by dose of maximum CRT in pediatric CNS tumor survivors.

Table 1

Demographics of childhood cancer survivors and sibling control group followed by the CCSS

Characteristics	All Diagnosis* No./Total (%); *P* Value †	CNS* No./Total (%); *P* Value †	Siblings* No./Total (%)
Alive††:	12,286/14,358 (85.6); *P*<0.0001	1,476/1,876 (78.7); *P*<0.0001	4,006/4,023 (99.6)
Female:	6,645/14,358 (46.3); *P*<0.0001	843/1,876 (44.9); *P*<0.0001	2,086/4,023 (51.9)
Race:			
White non Hispanic	11,943/14,288 (83.6)	1,610/1,869 (86.1)	3,509/3,874 (90.6)
Black non Hispanic	668/14,288 (4.7)	73/1,869 (4.0)	112/3,874 (2.9)
Hispanic/Latino	313/14,288 (2.2)	32/1,869 (1.7)	61/3,874 (1.6)
Other	1,364/14,288 (9.5)	154/1,869 (8.2)	192/3,874 (5.0)
	P<0.0001	*P*=0.12	
Age at diagnosis:			
0–4	5,753/14,358 (40.1)	644/1,876 (34.3)	-
5–9	3,201/14,358 (22.3)	555/1,876 (29.6)	-
10–14	2,913/14,358 (20.3)	461/1,876 (24.6)	-
15–20	2,491/14,358 (17.3)	216/1,876 (11.5)	-
Age at last follow up:			
<18	1,263/14,358 (8.8)	214/1,876 (11.4)	255/4,023 (6.3)
18–29	5,101/14,358 (35.5)	690/1,876 (36.8)	1,242/4,023 (30.9)
30–39	5,054/14,358 (35.2)	668/1,876 (35.6)	1,360/4,023 (33.8)
40+	2,940/14,358 (20.5)	304/1,876 (16.2)	1,166/4,023 (29.0)
	P<0.0001	*P*<0.0001	
Tumor recurrence:	2,306/14,358 (16.1)	379/1,876 (20.2)	-
Max CRT dose:			
0 Gy	4,85/12,079 (33.8)	473/1,554 (30.4)	-
1.5–29 Gy	2,756/12,079 (22.8)	10/1,554 (0.6)	-
30–49 Gy	533/12,079 (4.4)	222/1,554 (14.3)	-
50+ Gy	955/12,079 (7.9)	811/1,554 (52.2)	-
Indirect Radiation	3750/12,079 (31.0)	38/1554 (2.4)	-
Neck Irradiation (yes):	2,932/12,091 (24.2)	426/1,562 (27.3)	
Treatment with alkylating agent:	6,826/12,560 (54.3)	411/1,651 (24.9)	-
Known Stroke RF‖:			
HTN	2,206/14,170 (15.6); *P*<0.0001	187/1,836 (10.2); *P*=0.52	429/4,000 (10.7)
OCP use	3,873/6,546 (59.2); *P*=0.09	435/828 (52.5); *P*<0.0001	1,259/2,057 (61.2)
Diabetes	589/14,125 (4.2); *P*<0.0001	56/1,828 (3.1); *P*=0.23	100/3,998 (2.5)
History of smoking	3,868/13,594 (28.5); *P*<0.0001	359/1,773 (20.2); *P*<0.0001	1,600/3,941 (40.6)
Neurofibromatosis type 1	57/14,358 (0.4); *P*=0.015	40/1,876 (2.1); *P*<0.0001	8/4,023 (0.2)

Abbreviations: CCSS: Childhood Cancer Survivor Study; CNS: Central Nervous System; CT: chemotherapy; CRT: cranial radiation therapy; HTN: hypertension; Max: maximum; OCP: oral contraceptive.

Each row lists only study participants with available data for each specified factor.

*Maximum number of cancer survivors included in this study n=14,358; CNS tumor survivors n=1,876 and siblings n=4,023;

†Compared to siblings;

††Alive at last follow up (2007–2009);

‖Prior to stroke or last follow up.

Table 2

Rate and Relative Risk of Late-Occurring First Stroke * in Cancer Survivors followed by CCSS compared to Sibling Control Group

Disease	N†	# Late-occurring Strokes	Raw Rate per 100,000 person-year (95% C.I.)	Age Adjusted Rate per 100,000 person-year †† (95% C.I.)	RR (95%C.I.)	*P* Value
All Survivors	14,186	292	112.2 (99.9 – 126.2)	77.4 (62.3 – 96.2)	7.8 (4.7 – 13.0)	<0.0001
CNS	1,810	125	412.6 (346.2 – 491.7)	291.6 (207.9 – 408.9)	30.1 (17.9 – 50.8)	<0.0001
Leukemia	4,763	71	82.6 (65.2 – 104.7)	49.3 (31.1 – 78.1)	8.2 (4.6 – 14.5)	<0.0001
Neuroblastoma	946	5	27.7 (7.5 – 102.7)	13.4 (2.0 – 87.3)	5.2 (1.1 – 24.4)	0.04
Soft tissue sarcoma	1,241	18	75.9 (47.6 – 120.9)	81.6 (37.6 – 177.0)	4.6 (2.3 – 9.2)	<0.0001
HL	1,925	44	120.8 (89.9 –162.4)	29.1 (11.4 –74.1)	4.4 (2.5 –7.8)	<0.0001
Kidney (Wilms)	1,250	6	25.3 (7.2 –88.4)	36.4 (7.3 –182.7)	3.3 (0.8 –13.3)	0.09
Bone cancer	1,183	14	62.5 (36.4 –107.4)	86.7 (37.4–200.7)	2.8 (1.3 –5.8)	0.007
NHL	1,068	9	45.4 (23.0 –89.6)	7.1 (0.8 –63.9)	2.6 (1.2 –5.9)	0.02
Sibling control //	4,018	17	13.8 (8.5 –22.5)	9.3 (3.7 –23.1)	Reference	

Abbreviations: HD: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma; RR= Relative risk adjusted for current age and gender.

* Late-occurring stroke defined as any stroke after enrollment in CCSS at 5 years post-diagnosis.

† Number at risk at study entry excludes those with prior stroke

†† Adjusted rates indicate predicted rate at median age of 23 for females to compare across disease groups.

// For sibling controls strokes were counted starting at age 5 years.

Table 3

Multivariate Hazard Ratio of First Late-Occurring Stroke * in Pediatric Cancer Survivors followed by the CCSS (n=14,186)

	Model I †		Model II †	
Characteristic	**HR (95% C.I.)**	***P* Value**	**HR (95% C.I.)**	***P* Value**
Age at diagnosis (years):				
0–4 vs. 15–20	0.8 (0.5 – 1.3)	0.35	0.8 (0.5 – 1.3)	0.38
5–9 vs. 15–20	0.9 (0.6 – 1.4)	0.65	0.9 (0.6 – 1.4)	0.73
10–14 vs. 15–20	0.8 (0.6 – 1.3)	0.39	0.8 (0.6 – 1.2)	0.38
Male vs. female:	1.0 (0.8 – 1.4)	0.78	1.0 (0.8 – 1.4)	0.76
Max CRT dose:				
50+ Gy vs. none	11.0 (7.4 – 16.5)	<0.0001	11.0 (7.4 – 16.5)	<0.0001
30–49 Gy vs. none	5.9 (3.5 – 9.9)	<0.0001	5.9 (3.5 – 9.9)	<0.0001
1.5–29 Gy vs. none	1.8 (1.2 – 2.8)	0.01	1.8 (1.1 – 2.8)	0.01
Indirect radiation vs. none	1.2 (0.8 – 1.8)	0.48	1.2 (0.8 – 1.8)	0.41
Known stroke RF:				
HTN vs. none	4.0 (2.8 – 5.5)	<0.0001	n/a	
Diabetes vs. none	1.5 (0.8 – 2.6)	0.17	1.4 (0.8 – 2.5)	0.21
Recurrence vs. none:	2.1 (1.5 – 2.9)	<0.0001	2.1 (1.5– 2.9)	<0.0001
Race:				
Black non-Hispanic vs. White non-Hispanic	1.7 (0.9 – 3.2)	0.10	n/a	
Other race/ethnicity vs. White non-Hispanic	1.3 (0.9 – 1.9)	0.17	n/a	
White, HTN vs. white, no HTN	n/a		3.8 (2.7 – 5.5)	<0.0001
Black, HTN vs. white, no HTN	n/a		15.9 (6.9 – 36.6)	<0.0001
Black, no HTN vs. white, no HTN	n/a		1.0 (0.4 – 2.5)	0.95
Other race, HTN vs. white, no HTN	n/a		4.1 (1.8 – 9.5)	<0.001
Other race, no HTN vs. white, no HTN	n/a		1.4 (0.9 – 2.1)	0.14

Abbreviations: CRT: Cranial radiation therapy; HTN: hypertension; HR: Hazard ratio; max: maximum; n/a: not applicable; RF: risk factor.

* Late-occurring stroke defined as any stroke after enrollment in CCSS at 5 years post-diagnosis.

† In model I and II diabetes, HTN, age at diagnosis, gender, and race were included as a priori factors. Recurrence, diabetes and HTN were treated as time-dependent variables. For model II a race/HTN composite was developed to demonstrate the interaction between race and HTN (P= 0.06).

Table 4

Multivariate Hazard Ratio of First Late-Occurring Stroke * in CNS Tumor Survivors followed by the CCSS (n=1810)

Characteristic	HR (95% C.I.)	*P* value
Age at diagnosis (years):		
0–4 vs. age 15–20	1.6 (0.7 – 3.8)	0.31
5–9 vs. age 15–20	1.7 (0.8 – 3.6)	0.21
10–14 vs. age15–20	1.4 (0.6 – 2.9)	0.43
Male vs. Female	1.1 (0.7 – 1.7)	0.63
Race/Ethnicity:		
Black non-Hispanic vs. White non-Hispanic	1.6 (0.6 – 4.2)	0.34
Other race/ethnicity vs. White non-Hispanic	1.4 (0.8 – 2.5)	0.29
Maximum CRT dose:		
50+ Gy vs. none	2.8 (1.5 – 5.3)	0.001
1.5–49 Gy vs. none	1.7 (0.7 – 3.8)	0.21
Indirect radiation	2.1 (0.6 – 7.5)	0.25
Any alkylating agent vs. none	2.0 (1.3 – 3.2)	0.002
Known Stroke RF †:		
Diabetes and HTN vs. neither	14.4 (5.7 – 36.2)	<0.0001
Diabetes, no HTN vs. neither	0.7 (0.1 – 5.2)	0.74
HTN, no diabetes vs. neither	2.9 (1.6 − 5.3)	<0.001

Abbreviations: CRT: Cranial radiation therapy; HR: Hazard ratio; HTN: Hypertension; RF: Risk factor.

* Late-occurring stroke defined as any stroke after enrollment in CCSS at 5 years post-diagnosis. Diabetes, HTN, age at diagnosis, gender, and race were included as a priori factors in the multivariable model. Recurrence, diabetes and HTN were treated as time-dependent covariates.

† A composite variable of HTN and diabetes was generated to present interaction of HTN and diabetes (p=0.057).